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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,209	12/08/2003	Amy L. Rubinstein	26007.0003U2	4631

23859 7590 02/12/2007
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SUITE 1000
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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,209	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 16-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/2/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-5 and 11-35 are pending. Claims 1, 2 and 5 are amended by Applicant amendment, filed 11/13/2006. Claims 6-10 were previously canceled by amendment filed 9/29/2006.

Election/Restrictions

2. Applicant's election with traverse of Group III, claims 11-15, drawn to method of identifying a blood vessel related gene that is involved in blood vessel growth comprising a zebrafish with an altered blood vessel related gene with that of a control and determine if the blood vessel related gene is involved in blood vessel growth, in the reply filed on 9/29/2006 is acknowledged. The traversal is on the ground(s) that Examiner has not proven that the search of the groups would be an unreasonable search burden and since all the groups are in the same class they should not be a search burden. This is not found persuasive for the following reasons.

The search of the different groups would be considered a search burden because the search strategy would be different even though they are classified together. Because of the significant reliance upon the non-patent literature in examination of the biotechnology art, applications are rarely searched by classification and are more commonly search by terminology, therefore search burden is based upon additional or different terms that must be added to the search query. In the instant case, the searches would not be coextensive. Group I would require search of

additional terms such as compound screen, anti-angiogenic, and pro-angiogenic that would need to be search in several different databases, therefore resulting in multiple additional searches. Furthermore, the search of the Group III would not require such terms to be search but will require the search of other terms, such as blood vessel related gene and altered. This level of additional and non-coextensive search is consider undue and would be considered a search burden for the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-5 and 16-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/29/2006.

Claims 11-15 are under consideration.

Information Disclosure Statement

3. The information disclosure statement (IDS) was filed on 9/02/2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

There is a list of references on pages 29-32. If Applicant wants these references formally considered. They must be submitted in an supplemental IDS.

Non-Compliant Amendment

4. It is noted that claims 2 and 5 are presented as "original". However, these claims have been amended and should have been indicated with the proper status identifier "Withdrawn-currently amended". A Notice of Non-Compliant amendment was mailed to Applicant on 10/10/2006, because claims 2 and 5 depended upon claim 0 and there was no claim 0 present. Applicant amended these claims to designate proper dependency in an amendment, filed 11/13/2006, however, they did not designate the proper claim status, which is also grounds for a Non-Compliant Amendment. However, because the dependency is clear and in the interest of compact prosecution, Applicant will only be put on notice of the Non-Compliance Amendment and prosecution will continue. Upon subsequent amendment to the claims, these claims should be indicated as "Withdrawn" or "Withdrawn-currently amended" to identify the correct status of the claims that were present in the amendments, filed 11/13/2006. Appropriate correction is required.

Sequence Non-Compliance

5. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

There are sequences present on pages 19 and 22 of the specification that do not have a corresponding Sequence Listing, CRF, or SEQ ID NOS.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for:

A method for identifying a blood vessel related gene that is involved in blood vessel growth comprising: a) providing a first transgenic zebrafish expressing a fluorescent reporter protein in blood vessels and a second transgenic zebrafish expressing a fluorescent reporter protein in blood vessels and additionally comprising an altered gene that results in altered gene product activity; and b) determining whether the altered gene has an effect on blood vessel growth by comparing blood vessel morphology of said first transgenic zebrafish to blood vessel morphology of said second transgenic zebrafish, wherein a difference in blood vessel morphology is indicative of a blood vessel related gene involved in blood vessel growth;

does not reasonably provide enablement for:

a method of identifying a blood vessel related gene that is involved in blood vessel growth comprising comparing 1) any measurable characteristic other than blood vessel growth, a transgenic zebrafish containing blood vessels that express 2) any reporter gene with a transgenic zebrafish containing blood vessels that express any reporter gene and has an 3) alteration in a blood vessel related gene that does not result in an altered gene product activity and determining the effect of the altered blood vessel related gene on blood vessel growth such that if there is 1) any difference between the blood vessels of the transgenic zebrafish, the blood vessel related gene is involved in blood vessel growth.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses a transgenic zebrafish that expressed green coral reef fluorescent protein (CGFP) operably linked to the VEGFR2 promoter to target GFP expression to its blood vessels to allow for the visualization of zebrafish embryo blood vessel development in vivo (p. 20-21 and Fig 1). The specification also teaches that these zebrafish can be used to identify blood vessel related gene in zebrafish by a) a constructing a zebrafish blood vessel cDNA library and b) identifying a blood vessel related gene (p. 13, lines 12-15) and then upon identification of a blood vessel related

gene, altering the blood vessel related gene in a zebrafish having a blood vessel specific CGFP expression (p. 13, last par and p14, par 1 and 2).

However, the specification does not support the full breadth of the claims.

1) The preamble and the overall intent of the claims is to be a method of identifying a blood vessel related gene that is involved in blood vessel growth. However, method step of a) (claim 11, line 3) solely states "comparing" the two different transgenic zebrafish without stating what is to be compared. Again later in the same claim, the method step of b) is determining the effect of the alter blood vessel related gene on growth by stating "a difference between the blood vessels" (line 6).

However, not any difference in the blood vessels and any comparison between the zebrafish will identify a blood vessel related gene involved in blood vessel growth. Only measurements of blood vessel growth will identify blood vessel genes involved in blood vessel growth. Therefore, an artisan would not know how to use or make the instant method to identify a blood vessel related gene involved in blood vessel growth without having a step that actually measures blood vessel growth specifically.

2) The breadth of the claims are drawn to the use of any reporter gene/protein. However, the claimed novelty of the instant invention is the use of a fluorescent reporter gene which will allow for in vivo assays in the zebrafish (p. 2 last par). The art also suggests that the use of a fluorescent reporter gene will be an improvement of other reporter genes such as LacZ, because the fluorescent reporter gene can be visualized in vivo and will better visualize vessels (Motoike et al. Genesis 28:78, col 1, lines 1-16, 2000; of record in IDS). Therefore, for an artisan to utilize the novel improvement

proposed by the instant invention, they would specifically need to use a fluorescent reporter gene to visualize differences in blood vessel growth and development. Furthermore, an artisan would not know how to use a reporter gene that does not allow for in vivo detection in this the claimed invention as disclosed by the specification.

3) The breadth of the claims are drawn to any type of any alteration to a blood vessel related gene. However, not all alteration that can be made to a blood vessel related gene will result in an alteration in gene product activity. The specification does not go into great detail about methods of altering a blood vessel related gene, however, several methods of doing so are established in the art. The breadth of the claims encompass altering a blood vessel related gene in a manner that does not alter gene product activity and therefore is a silent alteration. Because this assay relies upon the alteration that result in an a phenotypic difference that is a result in an alteration in gene product activity of the alter gene, an artisan would not be able to use the instant assay with an altered gene that did not have an alteration that resulted in an alteration in gene product activity, because the artisan would not be able to determine a phenotypic difference in blood vessel growth and therefore would not be able to determine if the altered gene is involved in blood vessel growth as is required by the claims.

Therefore, the instant invention, as claimed, is not enable for the full breadth of the claims because the great breadth of the claims not being supported by the specification. Therefore, the instant invention is only enabled for A method of identifying a blood vessel related gene that is involved in blood vessel growth comprising: a) providing a transgenic zebrafish comprising an altered blood vessel related gene,

wherein its nucleic acid sequence has been altered and its expression has also been altered, and comprising a fluorescent reporter gene construct operably linked to a promoter that drives expression in blood vessels and providing another transgenic zebrafish comprising a fluorescent reporter gene construct operably linked to a promoter that drives expression in blood vessels, b) comparing blood vessel growth by visual analysis of the fluorescent blood vessels in vivo in the transgenic zebrafish with the altered blood vessel related gene to fluorescent blood vessel growth in the transgenic zebrafish without the altered blood vessel related gene, and d) determining the effect of the altered blood vessel related gene on blood vessel growth, wherein a difference in blood vessel growth between the transgenic zebrafish with the altered blood vessel related gene and the transgenic zebrafish without the altered blood vessel related gene identifies a blood vessel related gene involved in blood vessel growth.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 recites, " identifying a blood vessel related gene that is involved in blood vessel growth". Then step (a) recites, "comparing transgenic zebrafish", one with an altered blood vessel related gene and one that does not have the altered gene.

Therefore, this step suggests that the method is comparing alteration of a gene. However, this does not coincide with preamble which states that the method is identifying a gene involved in both vessel growth, hence determining a difference in blood vessel growth brought about by a gene alteration, not gene alteration itself. Therefore, it is not clear from the claims if the method is meant to determine differences in blood vessel growth or gene alteration. Therefore, the metes and bounds of the claim are indefinite.

Claims 12-15 depend upon claim 11, which has been deemed indefinite. Therefore, claims 12-15 are rendered indefinite.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Motoike et al (Genesis 28:75-81, 2000; of record in IDS).

The instant invention is drawn to a method of identifying a blood vessel related gene involved in blood vessel growth comprising comparing a transgenic zebrafish comprising a reporter gene and an altered blood vessel related gene to a transgenic zebrafish comprising the reporter gene only (claim 11). Narrowing embodiments specify that the reporter gene encode a fluorescent protein (claim 12).

Motoike et al disclose a transgenic zebrafish comprising a GFP reporter gene operably linked to the Tie2 promoter (par bridging p 76-77). Tie2 is a blood vessel specific gene that is expressed during blood vessel growth and development. Motoike

et al. disclose that transgenic zebrafish expressing the Tie2-GFP construct exhibit uniform expression of GFP in vascular endothelial cells (par bridging p 76-77) and that the zebrafish exhibited fluorescent vessels in developing embryos and throughout adulthood, allowing visualization of the general vascular patterns, growth, and development in single cell resolution (abstract). Motoike et al. also disclose that this zebrafish system will be a useful tool for the study of vascular development and that these zebrafish can be crossed to various existing mutant lines of zebrafish, which have altered vascular development, to investigate morphological changes in vascular growth and development (par bridging p.77-78). Because Motoike et al. disclose crossing the Tie2-GFP zebrafish with mutants that already exist, they are providing zebrafish with both the Tie2-GFP reporter gene and a known, altered blood vessel related gene as claimed. Because the Tie2-GFP is disclosed as being blood vessel specific to be used in assays of vascular growth and development, they also disclose the means of comparing the two zebrafish and identifying a blood vessel related gene involved in blood vessel growth.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoike et al. as applied to claims 11 and 12 above, and further in view of Matz et al (Nature 17:969-973, 1999; of record in IDS).

The instant claims further limit the method by specifying wherein the reporter protein is a green reef coral fluorescent protein (claim 13) or a red fluorescent protein (claim 14).

As disclosed above, Motoike et al teaches a transgenic zebrafish comprising a GFP reporter gene operably linked to the Tie2 promoter. Motoike et al do not specifically teach a green reef coral fluorescent protein or a red fluorescent protein.

However, Matz et al teaches clones of six fluorescent protein homologous to green fluorescent protein isolated from reef corals. They further disclose two of these have spectral characteristics different from GFP, emitting at yellow and red wavelengths. They are disclosed that they were used for in vivo labeling in mammalian cell culture and mRNA injection of fog embryos (abstract).

Therefore, at the time of filing it would have been obvious to make a transgenic zebrafish as taught by Motoike et al expressing a coral reef GFP or red fluorescence protein as taught by Matz et al. One would be motivated to use the coral reef GFP or red fluorescence protein because it would be useful in *in vivo* labeling experiments as taught by Matz et al. One would have a reasonable expectation of success because making GPF transgenic zebrafish was established in the art and the CGFPs are homologous and were used in *in vivo* labeling experiments in frog eggs and mammalian cells.

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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